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(54) **Thiazolidinone derivatives as hypoglycemic agents and for treating Alzheimer's disease.**

(57) Provided are methods for treating hyperglycemia and Alzheimer's disease utilizing certain rhodanine derivatives. Certain of the rhodanine derivatives utilized in the instant methods are novel and, accordingly, such compounds, process for preparing same and pharmaceutical formulations thereof, are also provided.

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The present invention relates to certain rhodanine derivatives, pharmaceutical formulations thereof, processes for preparing same, as well as methods of using such compounds to treat Alzheimer's disease and hyperglycemia.

5 Diabetes mellitus is a systemic disease characterized by disorders in the metabolism of insulin, carbohydrates, fats and proteins, and in the structure and function of blood vessels. The primary symptom of acute diabetes is hyperglycemia, often accompanied by glucosuria, the presence in urine of large amounts of glucose, and polyuria, the excretion of large volumes of urine. Additional symptoms arise in chronic or long standing diabetes. These symptoms include degeneration of the walls of blood vessels. Although many different organs are affected by these vascular changes, the eyes and kidneys appear to be the most susceptible. As 10 such, long-standing diabetes mellitus, even when treated with insulin, is a leading cause of blindness.

There are two recognized types of diabetes. Type I diabetes is of juvenile onset, ketosis-prone, develops early in life with much more severe symptoms and has a near-certain prospect of later vascular involvement. Control of this type of diabetes is difficult and requires exogenous insulin administration. Type II diabetes mellitus is of adult onset, ketosis-resistant, develops later in life, is milder and has a more gradual onset.

15 One of the most significant advancements in the history of medical science came in 1922 when Banting and Best demonstrated the therapeutic effects of insulin in diabetic humans. However, even today, a clear picture of the basic biochemical defects of the disease is not known, and diabetes is still a serious health problem. It is believed that two percent of the United States' population is afflicted with some form of diabetes.

20 The introduction of orally effective hypoglycemic agents was an important development in the treatment of hyperglycemia by lowering blood glucose levels. Oral hypoglycemic agents are normally used in the treatment of adult onset diabetes.

25 A variety of biguanide and sulfonylurea derivatives have been used clinically as hypoglycemic agents. However, the biguanides tend to cause lactic acidosis and the sulfonylureas, though having good hypoglycemic activity, require great care during use because they frequently cause serious hypoglycemia and are most effective over a period of ten years.

30 In Chemical & Pharmaceutical Bulletin, 30, 3563 (1982), Chemical & Pharmaceutical Bulletin, 30, 3580 (1982) and Chemical & Pharmaceutical Bulletin, 32, 2267 (1984), reference is made to a variety of thiazolidinediones which have blood glucose and lipid lowering activities. Antidiabetic activity of cigitazone was also reported in Diabetes, 32, 804 (1983). However, these compounds have proven difficult to use because of insufficient activities and/or serious toxicity problems.

35 Furthermore, Alzheimer's disease, a degenerative disorder of the human brain, continues to afflict more and more persons throughout the world. Such disease results in progressive mental deterioration manifested by memory loss, confusion, disorientation and the concomitant loss of enjoyment of life associated therewith. At the present time there is no scientifically recognized treatment for Alzheimer's disease. Because of this, and because of the debilitating effects of the disease, there continues to exist an urgent need for effective treatments.

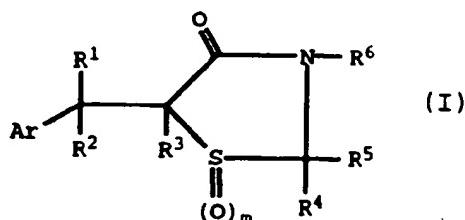
40 The present invention relates to a series of hypoglycemic agents which are capable of lowering blood glucose levels in mammals. Accordingly, one object of the present invention is to provide compounds having excellent hypoglycemic activity. The hypoglycemic agents of the present invention are believed to have minimal toxicological effects. It is, therefore, believed that the compounds of the present invention may be very useful for treating diabetes.

45 The present invention also relates to a series of compounds having cathepsin inhibitory activity. As will be discussed more fully below, compounds capable of inhibiting cathepsin (and, in particular, cathepsin D) may be useful for treating Alzheimer's disease. Accordingly, a further object of the present invention is to provide compounds which can be used to treat Alzheimer's disease.

50 Other objects, features and advantages of the present invention will become apparent from the subsequent description and the appended claims.

The present invention provides a method of reducing blood glucose concentrations in mammals comprising administering a therapeutically effective amount of a compound of formula (I)

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wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkylxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2-, or 3-thienyl, (vii) 2-, 3- or 4-pyridyl, (viii) 2- or 3-furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3-indolyl or (xiii) N-substituted 2- or 3-indolyl;

5 R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

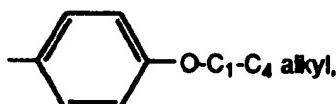
10 R² and R³ are each hydrogen or when taken together form a bond;

R⁴ and R⁵ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁵ is hydrogen, the other is -SCH₃;

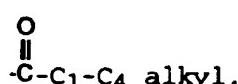
15 R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃, or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR⁸,



tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio, or



where R⁸ is hydrogen, C₁-C₄ alkyl or



35 R⁹ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy or NH₂, and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl), where q is an integer from 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring; and

40 m is 0, 1, or 2;

with the provisos that

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R¹

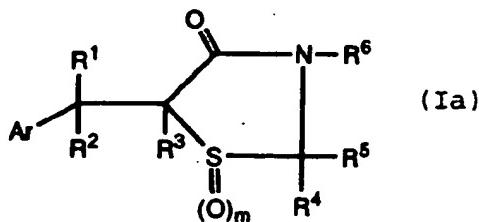
45 must be hydrogen;

Ar cannot be phenyl substituted solely with two hydroxy substituents; and

when R⁴ and R⁵ are each hydrogen, R⁶ cannot be C₁-C₆ alkyl,

or a pharmaceutically acceptable salt thereof, to a mammal in need of having its blood glucose concentration reduced.

50 The present invention also provides a method of treating Alzheimer's disease in a mammal suffering from or susceptible to such disease comprising administering a therapeutically effective amount of a compound of formula (Ia)



10 wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkyloxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl or (iii) 1- or 2-naphthyl;

15 R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

R² and R³ are each hydrogen or when taken together form a bond;

20 R⁴ and R⁵ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁵ is hydrogen, the other is -SCH₃;

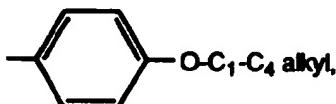
R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃, or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR⁸,

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tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio, or

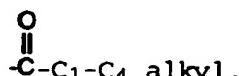
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where R⁸ is hydrogen, C₁-C₄ alkyl or

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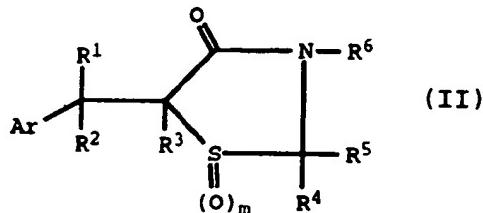


R⁹ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy or NH₂, and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl), where q is an integer from 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperizinyl, or N-methylpiperazinyl ring; and

m is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment.

50 Certain of the compounds which can be employed in the methods of the present invention are novel. As such, the present invention also provides novel compounds of the formula (II)



10 wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₂-C₄ alkylphenyl, NO₂, F; Cl, phenoxy, C₁-C₄ alkylloxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2-, 3- or 4-pyridyl, (viii) 2- or 3-furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3-indolyl or (xiii) N-substituted 2- or 3-indolyl;

15 R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

20 R² and R³ are each hydrogen or when taken together form a bond;

R⁴ and R⁵ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁵ is hydrogen, the other is -SCH₃;

25 R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃ or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is

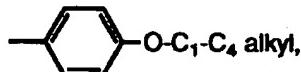
cyano, OR⁸,



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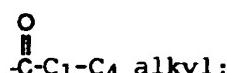
tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio or

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where R⁸ is hydrogen, C₁-C₄ alkyl, or

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45 R⁹ is hydrogen, C₁-C₄ alkyl or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, -(CH₂)_qS(C₁-C₄ alkyl), C₂-C₈ alkynyl, phenyl, or C₁-C₄ alkylphenyl, where q is 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl or N-methylpiperazinyl ring; and

m is 0, 1, or 2;

with the provisos that

50 when Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, F, Cl, trifluoromethyl, phenoxy, C₁-C₄ alkylloxyphenyl, C₁-C₈ alkylthio, NO₂, -N(R⁷)₂ or -COOR⁷, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2- or 3-indolyl, (viii) 2- or 3-furanyl, (ix) quinolinyl or (x) 2-, 3- or 4-pyridyl; R¹ is hydrogen or C₁-C₆ alkyl; R² and R³ taken together form a bond; m is 0; and R⁴ and R⁵ taken together are =S, R⁶ must be other than hydrogen or C₁-C₆ alkyl;

when Ar is phenyl; R¹ is hydrogen, methyl or ethyl; R² and R³ taken together form a bond; m is 0; R⁴ and R⁵ taken together are =S; R⁶ must be other than phenyl or C₁-C₄ alkylphenyl;

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R¹ must be hydrogen;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring; and when R⁴ and R⁵ are each hydrogen R⁶ cannot be C₁-C₆ alkyl,
and the pharmaceutically acceptable salts thereof.

In addition to the genus of novel compounds described by formula II, above, certain other of the compounds which can be employed in the methods of the present invention also appear to be novel. These compounds, while structurally similar to compounds specifically known in the art (see, for example, European Patent Application Nos. 343643, 391644 and 39817 as well as U.S. Patent No. 4,552,891), are not actually described in any of those patents or applications. As such, the present invention also encompasses the following novel compounds and their pharmaceutically acceptable salts:

- 5-[(2-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(4-fluorophenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(2-thienyl)methylene]-2-thioxo-4-thiazolidinone;
- 15 5-[(2-furanyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3,4,5-trimethoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone;
- 4-[(2-thioxo-4-thiazolidinone)methylene]benzoic acid;
- 5-[(3-hydroxy-4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-hydroxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone;
- 20 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-hydroxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-ethoxy-4-propoxyphe nyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 25 5-[(3,4-dipropoxyphe nyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[[3-(methyloxyphenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxy-phenyl)methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid;
- 5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 30 5-[(3-ethoxy-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[[3,5-bis(1-methylpropyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid;
- 5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-3-methyl-4-thiazolidinone;
- 5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 35 5-[(3,5-dimethoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
- 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
- 5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
- 5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-3-methyl-4-thiazolidinone;
- 5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid.

40 Certain of the above compounds and, in particular, 5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid; and 5-[[3,5-bis(1-methylpropyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid (especially the latter three compounds), appear to possess a surprising ability to lower blood glucose levels in mammals compared to structurally similar compounds known in the art. Because of such surprising activity, these compounds are particularly preferred compounds of the present invention.

45 In addition, 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone appears to possess a surprising ability to inhibit cathepsin D levels compared to structurally similar compounds known in the art. Because of such surprising activity, such compound is also a particularly preferred compound of the present invention.

50 Finally, the present invention also provides pharmaceutical formulations comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

55 As used herein, the term "C₁-C₈ alkyl" represents a straight or branched alkyl chain having from one to eight carbon atoms. Typical C₁-C₈ alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, and the like. The term "C₁-C₈ alkyl" includes within its definition the terms "C₁-C₄

"alkyl" and "C₁-C₈ alkyl".

"C₁-C₄ alkylphenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to a phenyl ring. Typical C₁-C₄ alkylphenyl groups include methylphenyl, ethylphenyl, n-propylphenyl, isopropylphenyl, n-butylphenyl, isobutylphenyl, and tert-butylphenyl.

5 The term "C₁-C₄ alkylthiophenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to a thiophenyl moiety. Typical C₁-C₄ alkylthiophenyl groups include methylthiophenyl, ethylthiophenyl, isobutylthiophenyl and the like.

In a similar fashion, the term "C₁-C₄ alkyloxyphenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to phenoxy moiety. Typical C₁-C₄ alkyloxyphenyl groups include 10 methoxyphenyl, ethoxyphenyl, propoxyphenyl and the like.

"C₁-C₈ alkoxy" represents a straight or branched alkyl chain having one to eight carbon atoms, which chain is attached to the remainder of the molecule by an oxygen atom. Typical C₁-C₈ alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentoxy, hexoxy, heptoxy, and the like. The term "C₁-C₈ alkoxy" includes within its definition the term "C₁-C₄ alkoxy".

15 "C₁-C₈ alkylthio" represents a straight or branched alkyl chain having one to eight carbon atoms, which chain is attached to the remainder of the molecule by a sulfur atom. Typical C₁-C₈ alkylthio groups include methylthio, ethylthio, propylthio, butylthio, tert-butylthio, octylthio and the like. The term "C₁-C₈ alkylthio" includes within its definition the term "C₁-C₄ alkylthio".

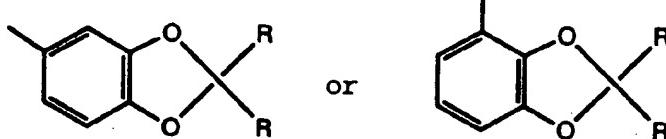
The term "C₂-C₆ alkenyl" refers to straight and branched chain radicals of two to six carbon atoms, both inclusive, having a double bond. As such, the term includes ethylene, propylene, 1-butene, 2-butene, 2-methyl-20 1-propene, 1-pentene, 2-methyl-2-butene and the like.

The term "C₂-C₆ alkynyl" refers to straight and branched chain radicals of two to six carbon atoms, both inclusive, having a triple bond. As such, the term includes acetylene, propyne, 1-butyne, 2-hexyne, 1-pentyne, 3-ethyl-1-butyne and the like.

25 The term "C₃-C₈ cycloalkyl" refers to saturated alicyclic rings of three to eight carbon atoms, both inclusive, such as cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like.

The terms "1,3-benzodioxanyl" and "substituted 1,3-benzodioxanyl" refer to structures of the formulae

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where each R is independently hydrogen or C₁-C₄ alkyl.

"Quinolinyl" refers to a quinoline ring system which is attached to the rest of the molecule at the 4, 5, 6, 7 or 8 position of such ring system.

40 "N-substituted 2- or 3- indolyl" refers to a 2- or 3- indolyl ring system substituted on the nitrogen atom of that ring system with a C₁-C₈ alkyl, C₁-C₄ alkylphenyl, or C₃-C₈ cycloalkyl group.

The term "pharmaceutically acceptable salts" refers to salts of the compounds of the above formulae which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the above formulae with a pharmaceutically acceptable mineral or organic acid, or a pharmaceutically acceptable alkali metal or organic base, depending on the types of substituents present on the compounds of the formulae.

45 Examples of pharmaceutically acceptable mineral acids which may be used to prepare pharmaceutically acceptable salts include hydrochloric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphorous acid and the like. Examples of pharmaceutically acceptable organic acids which may be used to prepare pharmaceutically acceptable salts include aliphatic mono and dicarboxylic acids, oxalic acid, carbonic acid, citric acid, succinic acid, phenyl-substituted alcanoic acids, aliphatic and aromatic sulfonic acids and the like. Such pharmaceutically acceptable salts prepared from mineral or organic acids thus include hydrochloride, hydrobromide, nitrate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, hydroiodide, hydrofluoride, acetate, propionate, formate, oxalate, citrate, lactate, p-toluenesulfonate, methanesulfonate, maleate, and the like.

50 Many compounds of formulae I, Ia or II which contain a carboxy, carbonyl, hydroxy or sulfoxide group may be converted to a pharmaceutically acceptable salt by reaction with a pharmaceutically acceptable alkali metal or organic base. Examples of pharmaceutically acceptable organic bases which may be used to prepare pharmaceutically acceptable salts include ammonia, amines such as triethanolamine, triethylamine, ethylamine,

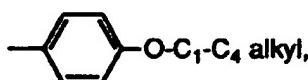
and the like. Examples of pharmaceutically acceptable alkali metal bases included compounds of the general formula MOR¹³, where M represents an alkali metal atom, e.g. sodium, potassium, or lithium, and R¹³ represents hydrogen or C₁-C₄ alkyl.

It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable and as long as the anion or cationic moiety does not contribute undesired qualities.

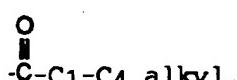
A preferred genus of compounds useful in the instantly claimed method of reducing blood glucose concentrations includes those compounds wherein Ar, R¹, R², R³, m, R⁴, and R⁵ are as set forth for formula I, and R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃ or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR⁸,



15 tetrazolyl, NR¹⁰R¹¹, -SH, -S(C₁-C₄ alkyl), or



20 where R⁸ is hydrogen, C₁-C₄ alkyl, or



30 R⁹ is hydrogen, C₁-C₄ alkyl, or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl) where q is 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring.

Of this preferred genus, those compounds in which m is 0 are more preferred.

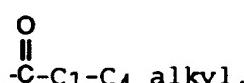
Of this more preferred genus, those compounds in which R⁴ and R⁵ taken together are =S are even more preferred.

35 Of this even more preferred genus, those compounds in which R¹ is hydrogen are especially preferred.

Of this especially preferred genus, those compounds in which R⁶ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is -OR⁸,



40 -NR¹⁰R¹¹, or C₁-C₄ alkylthio, where R⁸ is hydrogen, C₁-C₄ alkyl or



50 R⁹ is hydrogen, C₁-C₄ alkyl or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, or C₁-C₄ alkylphenyl are particularly preferred.

Of this particularly preferred genus, those compounds in which R⁶ is hydrogen, C₁-C₆ alkyl, or C₂-C₆ alkenyl are more particularly preferred.

55 Of this more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₆ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkyloxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 2-, 3- or 4-pyridyl, or (iv) 2- or 3-furanyl are substantially preferred.

Of this substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to

three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkylthiophenyl, -COOR⁷ or -N(R⁷)SO₂R⁷, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, are more substantially preferred.

5 Of this more substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl (especially C₁-C₄ alkyl), C₁-C₈ alkoxy (especially C₁-C₆ alkoxy), or hydroxy are even more substantially preferred.

10 The most preferred compounds which may be employed in the method of reducing blood glucose concentrations of the present invention include 5-[(3,4-diethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxy-phenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, sodium salt; 5-[(3-methoxy-4-pentoxyphenyl)methyl]-2-thioxo-4-thiazolidinone; 5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone and 5-[(3,5-dimethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone.

15 A preferred genus of compounds useful in the instantly claimed method of treating Alzheimer's disease includes those compounds wherein Ar, R¹, R², R³, m, R⁴ and R⁵ are as set forth for formula Ia, and R⁶ is hydrogen, C₁-C₆ alkyl or -(CH₂)_pY where p is 0, 1, 2 or 3 and Y is -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, phenyl or C₁-C₄ alkylphenyl.

20 Of this preferred genus, those compounds in which m is O are more preferred.

25 Of this more preferred genus, those compounds in which R⁴ and R⁵ taken together are =S are even more preferred.

30 Of this even more preferred genus, those compounds in which R² and R³ taken together form a bond are especially preferred.

35 Of this expecially preferred genus, those compounds in which Ar is phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkylxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₄ alkyl, are particularly preferred.

40 Of this particularly preferred genus, those compounds in which R¹ is hydrogen are more particularly preferred.

45 Of this more particularly preferred genus, those compounds in which Ar is phenyl substituted with from one to three substituents independently selected from phenoxy, phenyl, C₁-C₈ alkoxy, C₁-C₈ alkyl (especially C₁-C₄ alkyl), hydroxy, Cl, F, C₁-C₄ alkylthiophenyl, -N(R⁷)SO₂R⁷ and -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, are substantially preferred.

50 The most preferred compounds which may be employed in the method of treating Alzheimer's disease of the present invention include 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-hexoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl)methylene]-2-thioxo-4-thiazolidinone; and 5-[(4-(dimethylamino)phenyl)methylene]-2-thioxo-4-thiazolidinone.

55 A preferred genus of compounds of the present invention includes those compounds wherein Ar, R¹, R², R³, R⁴, R⁵ and R⁶ are as set forth for Formula II, and m is 0. Of this preferred genus, those compounds in which R⁴ and R⁵ taken together are =S are more preferred. Of this more preferred genus, those compounds in which R² and R³ taken together form a bond are especially preferred.

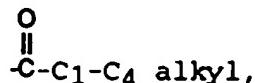
60 Of this especially preferred genus, those compounds in which R⁶ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(CH₂)_pY where p is 0, 1, 2, or 3 and Y is -OR⁸,

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65 -NR¹⁰R¹¹, or C₁-C₄ alkylthio, where R⁸ is hydrogen, C₁-C₄ alkyl or

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R^9 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl or NH_2 ; and R^{10} and R^{11} are each independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, phenyl, or $\text{C}_1\text{-C}_4$ alkylphenyl are particularly preferred.

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Of this particularly preferred genus, those compounds in which R^6 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_2\text{-C}_6$ alkenyl are more particularly preferred. Of this more particularly preferred genus, those compounds in which R^1 is hydrogen or phenyl are even more particularly preferred.

15

Of this even more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_8$ alkoxy, $\text{C}_1\text{-C}_8$ alkylthio, trifluoromethyl, $\text{C}_2\text{-C}_4$ alkylphenyl, NO_2 , F, Cl, phenoxy, $\text{C}_1\text{-C}_4$ alkoxyphenyl, thiophenyl, $\text{C}_1\text{-C}_4$ alkylthiophenyl, $-\text{COOR}^7$, $-\text{N}(\text{R}^7)\text{SO}_2\text{R}^7$ or $-\text{N}(\text{R}^7)_2$, where each R^7 is independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl, (iii) 1,3-benzodioxanyl, (iv) substituted 1,3-benzodioxanyl or (v) quinolinyl are substantially preferred compounds.

15

Of this substantially preferred genus, those compounds wherein Ar is (i) phenyl substituted with from one to three of phenoxy or $-\text{N}(\text{R}^7)\text{SO}_2\text{R}^7$, where each R^7 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl or (ii) 1,3-benzodioxanyl are more substantially preferred.

20

Certain preferred compounds of the present invention include 5-(diphenylmethylene)-2-thioxo-4-thiazolidinone; 5-[(1,3-benzodioxol-5-yl)methylene]-2-thioxo-4-thiazolidinone; 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-3-amino-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-3-dimethylamino-2-thioxo-4-thiazolidinone; and 5[(3-methanesulfonamidophenyl)methylene]-2-thioxo-4-thiazolidinone.

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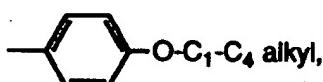
An alternative preferred genus of compounds of the present invention includes those compounds wherein Ar, $\text{R}1$, $\text{R}2$, $\text{R}3$, $\text{R}4$, $\text{R}5$, and m are as defined for formula II, and R^6 is $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $-\text{SO}_2\text{CH}_3$ or $-(\text{CH}_2)_p\text{-Y}$ where p is 0, 1, 2, or 3 and Y is cyano, $-\text{OR}^8$,

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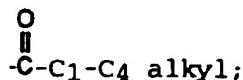
tetrazolyl, $-\text{NR}^{10}\text{R}^{11}$, $-\text{SH}$, $\text{C}_1\text{-C}_4$ alkylthio, or

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where R^8 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or



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R^9 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or NH_2 ; and R^{10} and R^{11} are each independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, phenyl, $\text{C}_1\text{-C}_4$ alkylphenyl, $-(\text{CH}_2)_q\text{OH}$, $-(\text{CH}_2)_q\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$, or $-(\text{CH}_2)_q\text{S}(\text{C}_1\text{-C}_4 \text{ alkyl})$ where q is 1 to 6, both inclusive, or R^{10} and R^{11} , taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring.

50

Of this preferred genus, those compounds in which m is 0 are more preferred.

Of this more preferred genus, those compounds in which R^4 and R^5 taken together are =S are even more preferred.

Of this even more preferred genus, those compounds in which R^2 and R^3 taken together form a bond are especially preferred

55

Of this especially preferred genus, those compounds in which R^6 is $\text{C}_2\text{-C}_6$ alkenyl, or $-(\text{CH}_2)_p\text{-Y}$ where p is 0, 1, 2, or 3 and Y is $-\text{OR}^8$,



5

-NR¹⁰R¹¹, or C₁-C₄ alkylthio, where R⁸ is hydrogen, C₁-C₄ alkyl or

10



C₁-C₄ alkyl, R⁹ is hydrogen, C₁-C₄ alkyl or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, or C₁-C₄ alkylphenyl are particularly preferred.

15 Of this particularly preferred genus, those compounds wherein R¹ is hydrogen or phenyl are more particularly preferred.

Of this more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₂-C₄ alkylphenyl, NO₂, F, Cl, phenoxy, C₁-C₄ alkoxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, 20 -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₈ alkyl (iii) 2-, 3- or 4-pyridyl, or (iv) 2- or 3-furanyl are even more particularly preferred.

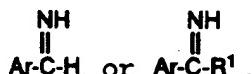
25 Of this even more particularly preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₂-C₄ alkylphenyl, NO₂, F, Cl, phenoxy, C₁-C₄ alkoxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₈ alkyl, are substantially preferred.

30 Of this substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl or C₁-C₈ alkoxy are most preferred.

The present invention also encompasses formulations comprising a compound of the present invention in combination with a pharmaceutically acceptable carrier, diluent, or excipient therefor. Preferred formulations of the present invention are those formulations which contain a preferred compound or genus of compounds of the present invention, as described above.

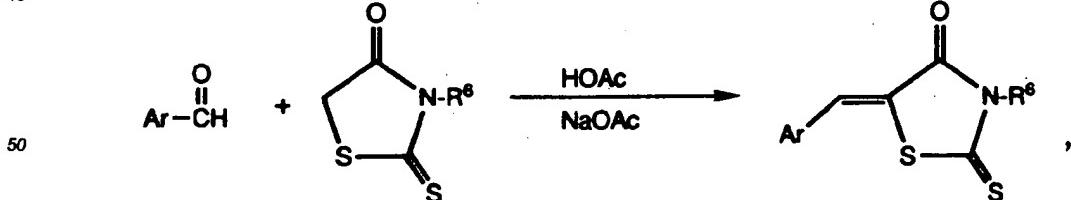
35 The compounds of the present invention, as well as the compounds employed in the methods of the present invention, can, typically, be prepared by methods well known to one skilled in the art of organic chemistry. For example, such compounds may be prepared by condensation of rhodanine, or an appropriately substituted rhodanine derivative, with an appropriately substituted aromatic aldehyde or aldehyde derivative such as a mono or disubstituted imine of the formula

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Such reaction is illustrated utilizing an appropriately substituted aromatic aldehyde as follows

45



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where Ar and R⁶ are as defined in formulae I, Ia and II.

55 Compounds of the present invention (as well as those compounds employed in the methods of the present invention) wherein R² and R³ are hydrogen, or when taken together form a bond, and R⁴ and R⁵ are each hydrogen can be prepared by subjecting the compound wherein R⁴ and R⁵ taken together form =S to catalytic hydrogenation. The relative proportions of compound obtained (R², R³, R⁴ and R⁵ all hydrogen vs. R² and R³

taken together form a bond and R⁴ and R⁵ are hydrogen) depends upon the temperature, pressure, and duration of hydrogenation, the solvent employed and the particular catalyst used. Alternatively, the above transformations may be accomplished by heating the compounds wherein R⁴ and R⁵ taken together are =S and R² and R³ taken together are a double bond in a mixture of hydrochloric acid and an alcohol, such as ethanol, in the presence of zinc. Reduction of the thione without affecting the benzylic double bond may be accomplished by heating the thione with a reducing agent such as tri-n-butyl tin hydride in a non-reactive solvent, such as toluene, and preferably in the presence of a free radical initiator, such as azobisisobutyronitrile. However, for such reduction to work, an N-substituted rhodanine substrate must be employed.

The transformation of compounds wherein R² and R³ taken together form a bond and R⁴ and R⁵ taken together are =S to those compounds wherein R² and R³ are both hydrogen while R⁴ and R⁵ remain unchanged may be accomplished by treating the unsaturated compound with a dihydropyridine, such as diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridine dicarboxylate in the presence of silica gel. The reaction is best carried out in the presence of a nonreactive solvent such as benzene or toluene, preferably under an inert atmosphere. The reaction may be accomplished at temperatures from about 25°C up to the reflux temperature of the mixture. At the preferred temperature of approximately 80°C, the reaction is essentially complete after about 12-18 hours.

Compounds of formulae I, Ia or II wherein R¹ is C₁-C₆ alkyl, phenyl, a substituted phenyl of the type described above, or C₁-C₄ alkylphenyl may be prepared by conventional Friedel-Crafts acylation of an appropriately substituted aromatic compound with an acyl halide of the formula R¹-C(O)-X, wherein R¹ is as defined in formulae I or II and X is chloro, fluoro, bromo or iodo. The resulting aromatic ketone is then condensed with rhodanine, or an appropriately substituted rhodanine derivative.

The compounds of the present invention (as well as the compounds employed in the methods of the present invention) allow various R⁶ substituents. These R⁶ substituents can be prepared as follows.

Compounds of formulae I, Ia and II wherein R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl or -(CH₂)_p-Y where p is as defined for formulae I, Ia and II and Y is cyano, or NR¹⁰R¹¹ where R¹⁰ and R¹¹ are each independently hydrogen or C₁-C₆ alkyl may be prepared using the method set forth in the above reaction scheme. Alternatively, rhodanine may be used for condensation with an aldehyde or aldehyde derivative forming those species wherein R⁶ is hydrogen, followed by alkylation or acylation with the appropriate R⁶-containing halide. The alkylation or acylation is usually accomplished in an inert solvent such as tetrahydrofuran or dimethylformamide and in the presence of a strong base such as sodium hydride.

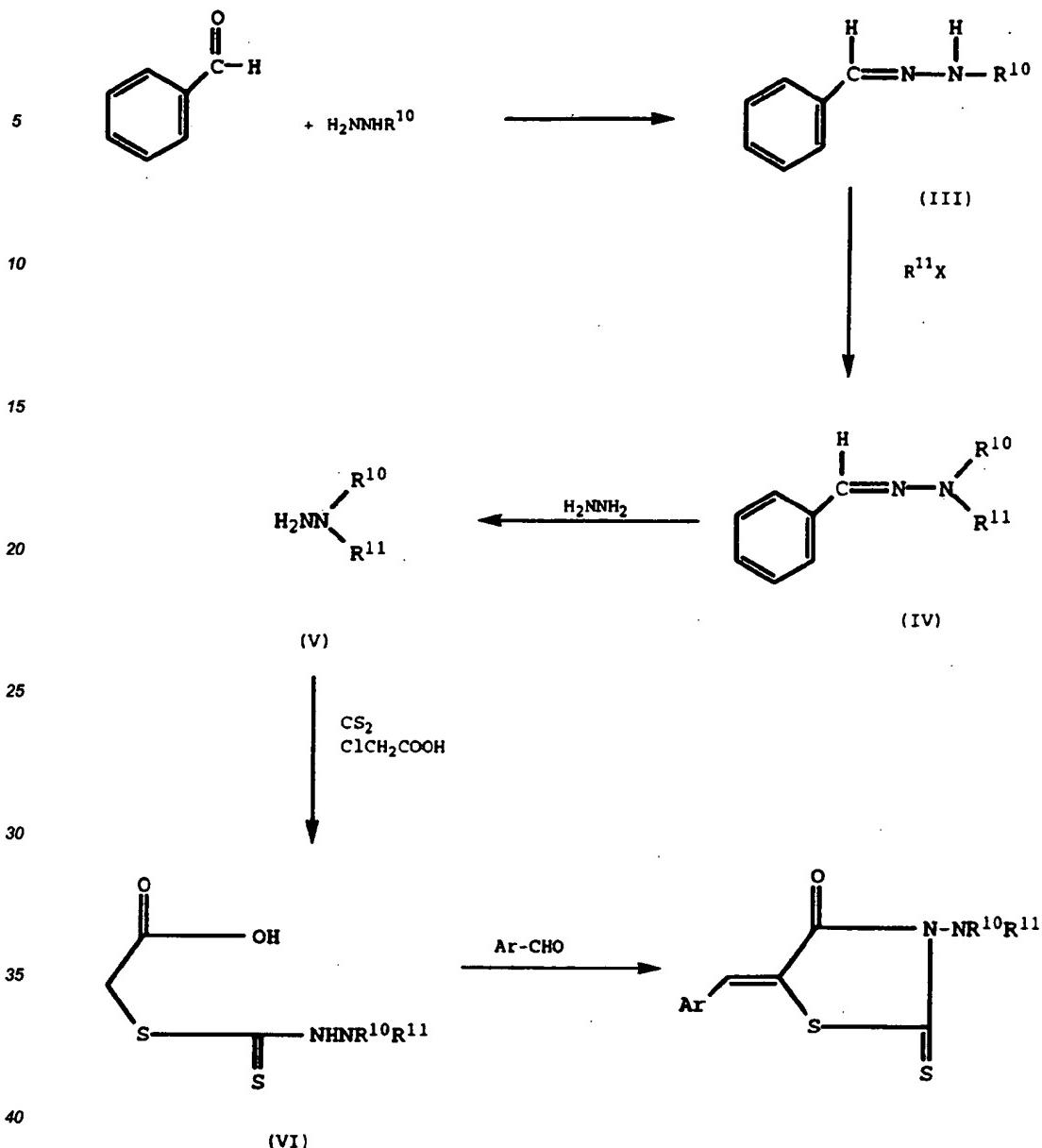
Alternatively, compounds of formulae I, Ia and II wherein R⁶ is -(CH₂)_p-Y where Y is cyano may be prepared by treating the non-cyanated analog with a halo-substituted aliphatic nitrile. From this cyano derivative the tetrazolyl is prepared as by treatment with tri-N-butyl tin azide in, for example, ethylene glycol dimethyl ether.

Compounds of formulae I, Ia and II wherein R⁶ is -(CH₂)_p-Y (p=0) and Y is NR¹⁰R¹¹, where R¹⁰ and R¹¹ are as defined in formulae I, Ia and II, may also be prepared by employing an appropriately substituted hydrazine. In this reaction sequence, benzaldehyde is reacted with an appropriately substituted hydrazine, in an alcoholic solvent, yielding III. An appropriately substituted alkyl halide is then reacted with III, in the presence of triethylamine and acetonitrile, to provide IV, which is then further reacted with hydrazine to yield the R¹⁰, R¹¹ hydrazine V. Compound V may alternatively be prepared by the reduction of a nitroso-R¹⁰R¹¹ amine using zinc dust and acetic acid or aluminum and a strong base. The R¹⁰, R¹¹ hydrazine is then treated with carbon disulfide, chloroacetic acid and triethylamine to provide intermediate VI. Condensation of VI with an appropriately substituted aromatic aldehyde or aldehyde derivative yields the desired product, as represented by the following reaction scheme.

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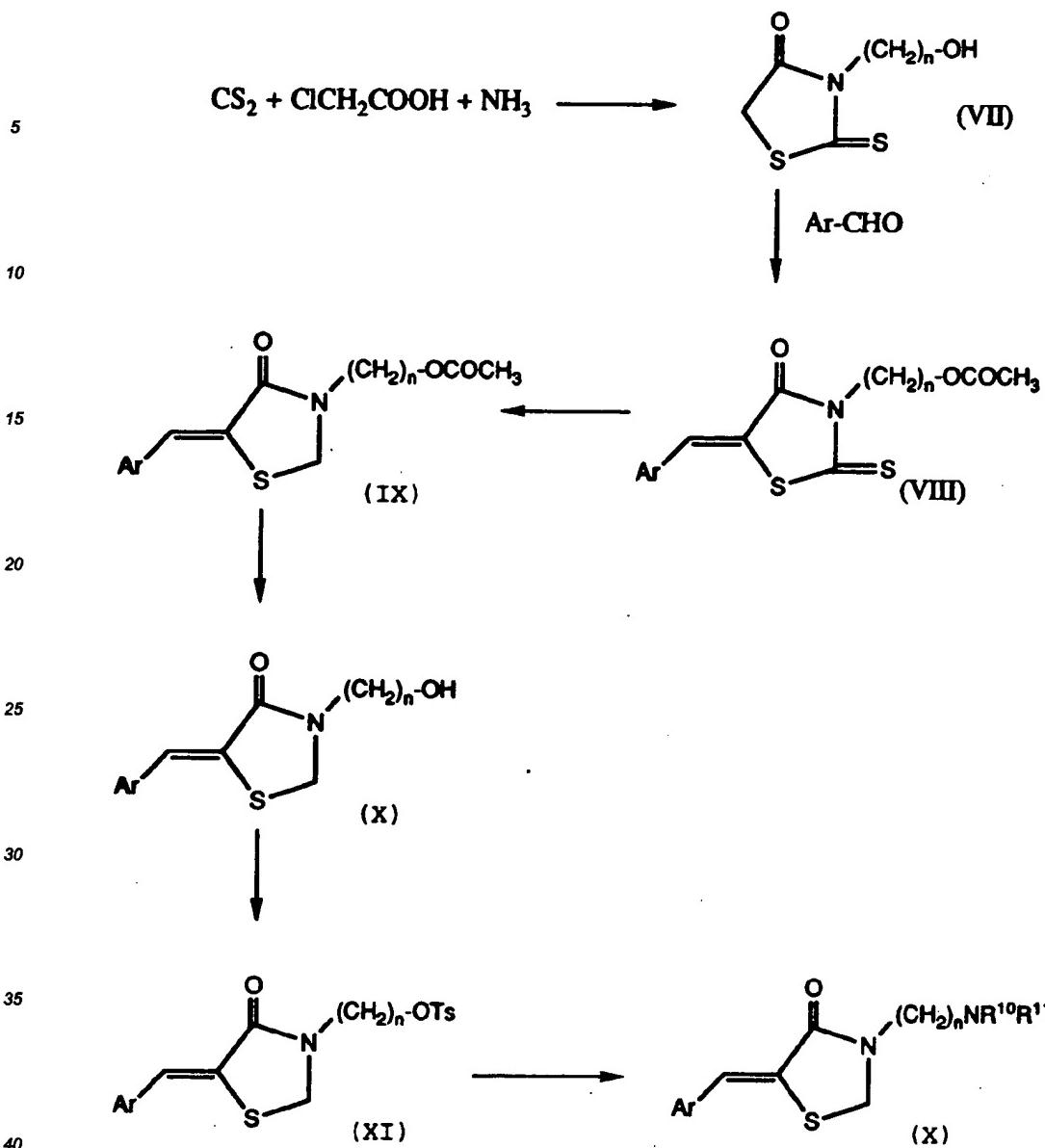
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Furthermore, the thione portion of the compound produced above may be reduced by treatment with a reducing agent such as tri-n-butyltin hydride in an inert solvent such as toluene, preferably in the presence of a free radical initiator such as azobisisobutyronitrile. Preparation of compounds wherein one of R¹⁰ and R¹¹ is hydrogen may be effected before or after reduction of the thione, as desired, by heating the disubstituted compound in a mixture of ethanol/water in the presence of a catalyst such as a rhodium catalyst.

Compounds of formulae I, Ia and II wherein R⁶ is -(CH₂)_p-Y and Y is OR⁸ or NR¹⁰R¹¹ (where R⁸ is hydrogen, acetyl or tosyl and R¹⁰ and R¹¹ are each independently hydrogen or C₁-C₆ alkyl) may also be prepared according to the following reaction scheme:



where Ts = Tosyl

A hydroxyalkyl rhodanine is prepared by condensing carbon disulfide, chloroacetic acid, and the appropriate hydroxyalkylamine by standard techniques. When condensed with the appropriately substituted aromatic aldehyde (or aldehyde derivative), as described above, the resulting product is the condensed 2-thioxo-4-thiazolidinone VIII which has been transformed into the acetyl derivative. The thioxo compound VIII may optionally be converted to the methylene compound of formulae I or II as described above. The acetyl group of intermediate IX may be removed upon treatment with aqueous ammonia in a solvent such as acetonitrile to provide compound X. The hydroxy compound X is then converted to the tosyl derivative upon treatment with p-toluenesulfonyl chloride in pyridine, preferably at temperatures of around 0°C. The versatile tosyl intermediate XI may then be transformed into the compounds of formulae I or II upon treatment with an appropriate $\text{HNR}^{10}\text{R}^{11}$ amine. This latter transformation is best accomplished by allowing XI to react in the presence of a molar excess of the amine. Once again, a solvent such as acetonitrile is useful for accomplishing this transformation.

Those compounds where m is 1 or 2 are readily prepared from the sulfide ($m=0$) by treatment with an oxidizing agent, such as m-chloroperbenzoic acid, in a suitable solvent for a time sufficient to generate the desired oxidative state.

Depending upon the definitions of R^1 , R^2 , and R^3 , the compounds of formulae I, Ia and II may exist in va-

rious isomeric forms. The compounds, formulations and methods of the present invention are not related to any particular isomer but include all possible isomers and racemates.

It will be readily appreciated by one skilled in the art that the aromatic portion of the compounds of the invention (or the compounds employed in the methods of the present invention) can be provided by compounds which are either commercially available or may be readily prepared by known techniques from commercially available starting materials. Similarly, the rhodanine or N-substituted rhodanine starting material is either commercially available or may be prepared by well known methods from commercially available substrates.

The following Examples illustrate the preparation of the compounds of the present invention, as well as compounds which may be employed in the methods of the present invention. The Examples are illustrative only and are not intended to limit the scope of the instant invention in any way.

Example 1

5-[(3-methanesulfonamidophenyl)methylene]-2-thioxo-4-thiazolidinone

Thirty seven grams (185.9 mmol) of 3-methanesulfonamidobenzaldehyde, 25.0 g (187.9 mmol) of rhodanine, 48.0 g (585.3 mmol) of anhydrous sodium acetate and 950 ml of acetic acid were stirred while heating at reflux for 20 hours. The reaction was then stirred at room temperature for approximately another 60 hours. The resulting slurry was poured into 3000 ml of a 1:1 ethanol/water mixture. Solids precipitated and were recovered by filtration, washed with water and then vacuum dried to provide 54 g of title compound. m.p. 260-265°C.

Analysis for C ₁₁ H ₁₀ N ₂ O ₃ S ₃				
Calculated:	C, 42.02;	H, 3.20;	N 8.91;	
Found:	C, 42.15;	H, 3.57;	N 8.71.	

Example 2

5-[(1,3-benzodioxol-5-yl)methylene]-2-thioxo-4-thiazolidinone

Twenty grams (133.2 mmol) of piperonal were reacted with 17.74 g (133.2 mmol) of rhodanine in 38.24 g (466.2 mmol) of glacial acetic acid at reflux for about 3 hours. The mixture was then poured into water and stirred overnight. A precipitate formed which was recovered by filtration and then air dried overnight to provide 27.8 g of title product. m.p. 194-195°C.

Analysis for C ₁₁ H ₇ N ₁ O ₃ S ₂ :				
Calculated:	C, 49.80;	H, 2.66;	N 5.28;	S, 24.17;
Found:	C, 50.04;	H, 2.38;	N 5.27;	S, 23.98.

Example 3

5-[(4-quinoliny)methylene]-2-thioxo-4-thiazolidinone

Rhodanine (2.2 g; 16.5 mmol), 1.3 ml of concentrated ammonium hydroxide and 1 g of ammonium chloride in 20 ml of ethanol were heated on a steam bath for 15 minutes. 4-Quinoline carboxaldehyde (2.6 g; 16.5 mmol) was added and the resulting mixture was heated on the steam bath for another hour. Upon cooling to 5°C a precipitate formed. This precipitate was recovered by filtration and then washed with water to provide 4 g of title compound, m.p. 325-328°C.

Analysis for C ₁₃ H ₈ N ₂ OS ₂ :				
Calculated:	C, 57.33;	H, 2.96;	N 10.29;	
Found:	C, 57.11;	H, 3.11;	N 10.21.	

Example 4**5-(diphenylmethylene)-2-thioxo-4-thiazolidinone**

One hundred and ninety grams (1.05 mol) of diphenyl ketimine, 140 grams (1.05 mol) of rhodanine, 5 ml of acetic acid and 1500 ml of toluene were heated at reflux for 3 hours. Crystals formed upon cooling. The solvent was decanted, fresh toluene was added to the residue and the resulting suspension was filtered. The recovered crystals were recrystallized from methanol to provide 172.0 g of title product, m.p. 192-194°C.

Analysis for C ₁₆ H ₁₁ NOS ₂ :					
10	Calculated:	C, 64.62;	H, 3.73;	O, 5.38;	N 4.71;
	Found:	S, 21.56;			
15	Calculated:	C, 64.13;	H, 3.84;	O, 5.57;	N 4.59;
	Found:	S, 22.38.			

Example 5**5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone**

A mixture of 9.9 g (50.0 mmol) of 4-phenoxybenzaldehyde, 6.8 g (51.1 mmol) of rhodanine, 15.5 g of sodium acetate and 60 ml of acetic acid was heated on a steam bath for two hours. The reaction solution was then poured into water causing crude product to precipitate. The precipitate was filtered and then washed successively with water followed by diethyl ether to provide 8.6 g of title product, m.p. 195-200°C.

Analysis for C ₁₆ H ₁₁ NO ₂ S ₂ :				
30	Calculated:	C, 61.32;	H, 3.54;	N 4.47;
	Found:	C, 61.07;	H, 3.63;	N 4.47.

The following compounds were synthesized using methods substantially equivalent to those described in Examples 1-5 above or as described elsewhere herein.

Example 6**5-(phenylmethylene)-2-thioxo-4-thiazolidinone, m.p. 202-203.5°C**Example 7**5-[(2-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 220-222°C**Example 8**45 5-[(4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 287-290°C**Example 9**5-[(2-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 197.5-199°C**50 Example 10**5-[(3-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 277-280°C**55 Example 11**5-[(3-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 242-244°C**

Example 12

5-[(2,4-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 253-255°C

5 Example 13

5-[(4-fluorophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 225-227°C

10 Example 14

5-[(2-thienyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 231-233°C

15 Example 15

5-[(2-furanyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 217-219°C

Example 16

5-[(4-pyridyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 297-298°C

20 Example 17

5-[(3,4,5-trimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 203-205°C

25 Example 18

5-[(4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 252-254°C

30 Example 19

5-[(3,4,5-trimethoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone, m.p. 210-213°C

Example 20

35 5-[(3-methoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 229-231°C

Example 21

5-[(4-methoxyphenyl)phenylmethylene]-2-thioxo-4-thiazolidinone, m.p. 169-171°C

40 Example 22

5-[(3-pyridyl)methylene]-2-thioxo-4-thiazolidinone, m.p. ~286°C

45 Example 23

5-[(3-chlorophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 233-235°C

50 Example 24

5-[(2,3-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 25

55 5-[(3-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 26

5-[(2-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

5 Example 27

5-[(3-methyl-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

10 Example 28

5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. ~260°C

15 Example 29

5-[(1,1'-biphenyl)-2-yl)methylene]-2-thioxo-4-thiazolidinone

20 Example 30

5-[(3-methoxy-4-hydroxyphenyl)methylene]-3-(2-propenyl)-2-thioxo-4-thiazolidinone, m.p. 146-148°C

25 Example 31

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 130-132°C

30 Example 32

5-[(3-ethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 217-217.5°C

35 Example 33

5-[(3-methylphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 197-202°C

40 Example 34

35 Example 35

5-[(2-naphthalenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 224-225°C

45 Example 36

5-[(3,4-dichlorophenyl)methylene]-2-thioxo-4-thiazolidinone

45 Example 37

4-[(2-thioxo-4-thiazolidinone)methylene]benzoic acid, m.p. ~320°C

50 Example 38

5-[(3,4-diethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

55 Example 39

5-[(1H-indol-3-yl)methylene]-2-thioxo-4-thiazolidinone

Example 40

5-[(3-hydroxy-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 218-220°C

5 Example 41

5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 175-176°C

10 Example 42

5-[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone, m.p. 245-250°C

15 Example 43

5-[(3-hydroxy-4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. ~224°C

20 Example 44

5-[(3-hydroxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone

25 Example 45

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 170-171°C

30 Example 46

5-[(3-hydroxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >225°C

35 Example 47

5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 158.5-160°C

40 Example 48

35 5-[(3-methoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 207-207.5°C.

45 Example 49

5-[(3-ethoxy-4-propoxyphe nyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 156-157°C

50 Example 50

5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 186.5-188°C

45 Example 51

5-[(3,4-dipropoxyphe nyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 167.5-168.5°C

50 Example 52

5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, sodium salt m.p. >225°C

55 Example 53

5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid, m.p. ~265°C

Example 54

5-[(3-methoxy-4-butoxyphenyl)methyl]-2-thioxo-4-thiazolidinone, m.p. 152-153.5°C

5 Example 55

5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >260°C

10 Example 56

5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

15 Example 57

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone sodium salt, m.p. ~254°C

20 Example 58

5-[(3-ethoxy-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >225°C

25 Example 59

5-[(3,5-bis(1-methylpropyl)-4-hydroxyphenyl)methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid, m.p. 191-193°C

30 Example 60

5-[(3,4-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

35 Example 61

5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 180°C

40 Example 62

5-[(3,5-dimethyl-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 260°C

45 Example 63

5-[(3,5-dimethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 230°C

50 Example 64

5-[(3-methoxy-4-pentoxyphenyl)methyl]-2-thioxo-4-thiazolidinone, m.p. 163-164°C

55 Example 65

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-3-methyl-4-thiazolidinone, m.p. 117-118°C

50 Example 66

5-[(3-methoxy-4-pentoxyphenyl)methylene]-4-thiazolidinone, m.p. 174-175°C

55 Example 67

5-[(3-methoxy-4-pentoxyphenyl)methyl]-4-thiazolidinone, m.p. 108-109°C

Example 68

5-[(3-methoxy-4-hexaoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

5 Example 69

5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 125-127°C

10 Example 70

5-[(3,5-dimethoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 166-167°C

15 Example 71

5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 181-184°C

20 Example 72

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 190-192°C

25 Example 73

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-3-methyl-4-thiazolidinone, m.p. 137°C

30 Example 74

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid
m.p. 202-206°C

35 Example 75

5-[(1-naphthyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 224-225°C

40 Example 76

5-[(2-naphthyl)methylmethylene]-2-thioxo-4-thiazolidinone

45 Example 77

5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

50 Example 78

45 5-[(3-phenoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone

55 Example 79

5-[[3-(methoxyphenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 177-180°C.

50 Example 80

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-3-amino-4-thiazolidinone, m.p. 118-121°C (dec).

55 Example 81

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-3-dimethylamino-4-thiazolidinone

Two hundred and fifty milligrams (1 mmol) of 3-methoxy-4-heptoxy benzaldehyde, 233 mg (1.2 mmol) of

2-(N-dimethylamino-dithiocarboxamido)acetic acid (a compound of formula VI, above), 330 mg (4 mmol) of anhydrous sodium acetate and 5 ml of acetic acid were stirred while heating at reflux for 15 hours. The reaction was then quenched by pouring the reaction solution into 10 ml of an ice/water mixture. The resulting solids were recovered by filtration, washed with ethyl acetate and then water to provide 450 mg of impure title compound. The impure compound was purified via recrystallization from hexane/methylene chloride to provide 180 mg of pure title compound. m.p. 105-108°C.

Example 82

10 5-[(4-(dimethylamino)phenyl)methylene]-2-thioxo-4-thiazolidinone

Example 83

5-[(4-heptoxyphenyl)methylene]-2-thioxo-3-dimethylamino-4-thiazolidinone, m.p. 80°C.

15 The present invention provides a method for lowering blood glucose levels in mammals comprising administering a therapeutically effective amount of a compound of formula I. The term "therapeutically effective amount", as defined herein, means the amount of compound necessary to provide a hypoglycemic effect following administration, preferably to a human susceptible to adult onset diabetes.

20 The hypoglycemic activity of the compounds of the present invention was determined by testing the efficacy of the compounds in vivo in male viable yellow obese-diabetic mice. The test procedure is described in detail below.

25 Test formulations were prepared by dissolving the test compound in a saline solution containing 2% Emulphor (a polyoxyethylated vegetable oil surfactant from GAF Corp.) to provide the dose level desired. Each test formulation was administered to six viable yellow obese-diabetic mice intraperitoneally at the beginning of the experiment. Blood glucose levels were determined immediately before the first dose and at 2 and 4 hours thereafter using glucose oxidase. A mean was taken of the 6 values obtained before the first dose and at the 2 and 4 hour intervals. The 2 and 4 hour mean values, calculated as a percentage of the first dose mean value, are reported in Table 1, below. In Table 1, Column 1 provides the example number of the test compound, Column 2 provides the dose level of compound tested, and Columns 3 and 4 provide a measurement of the test animal's 30 blood glucose level 2 and 4 hours after test compound administration, respectively, as a percentage of the test animal's pre-administration blood glucose level.

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TABLE 1

5 HYPOLYCEMIC ACTIVITY OF TEST COMPOUNDS IN
 10 OBESE DIABETIC MICE

	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level		After 4 hrs.
			After 2 hrs.		
15	1	50	82 ± 5		75 ± 2
20	2	50	96 ± 1		82 ± 3
25	3	50	90 ± 10		73 ± 3
30	4	50	91 ± 4		72 ± 7
35	5	50	79 ± 4		71 ± 3
40	6	50	85 ± 6		72 ± 4
45	6	50	92 ± 4		79 ± 4
50	7	50	80 ± 4		91 ± 7
55	8	50	94 ± 4		84 ± 6
60	9	50	91 ± 8		83 ± 6
65	10	50	89 ± 4		80 ± 4
70	11	50	84 ± 3		85 ± 6
75	12	50	90 ± 7		69 ± 6
80	13	50	94 ± 4		88 ± 5
85	14	50	84 ± 7		71 ± 8
90	15	50	73 ± 5		62 ± 4
95	16	50	94 ± 8		96 ± 9
100	17	50	88 ± 8		89 ± 10
105	18	50	89 ± 4		88 ± 5
110	19	50	85 ± 14		75 ± 4
115	20	50	76 ± 3		70 ± 5
120	21	50	99 ± 4		81 ± 6
125	22	50	77 ± 5		67 ± 2

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Table 1 (cont'd)

5	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
			After 2 hrs.	After 4 hrs.
10	22	50	77 ± 6	69 ± 6
	23	50	74 ± 6	90 ± 6
	24	50	78 ± 4	80 ± 5
15	25	50	78 ± 4	74 ± 4
	25	25	84 ± 5	87 ± 6
	26	50	80 ± 4	75 ± 2
20	27	50	93 ± 3	84 ± 6
	28	50	83 ± 9	79 ± 7
	29	50	84 ± 5	77 ± 6
25	30	50	78 ± 7	81 ± 5
	31	50	76 ± 7	76 ± 5
	32	50	75 ± 4	80 ± 8
30	32	50	80 ± 18	66 ± 11
	33	50	91 ± 6	86 ± 7
	34	50	85 ± 8	79 ± 9
35	35	50	83 ± 5	85 ± 6
	36	50	81 ± 7	90 ± 8
	37	50	89 ± 4	80 ± 4
40	38	50	60 ± 5	59 ± 4
	38	50	96 ± 6	80 ± 3
	38	50	86 ± 4	81 ± 5
45	38	25	69 ± 9	65 ± 7
	38	10	72 ± 4	71 ± 6
	38	10	73 ± 8	59 ± 7
50	39	50	83 ± 4	76 ± 4
	40	50	78 ± 5	72 ± 4

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Table 1 (cont'd)

5	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level					
			After 2 hrs.		After 4 hrs.			
	41	50	61	± 3		51	± 4	
10	41	50	64	± 6		54	± 5	
	41	50	77	± 5		62	± 5	
	41	50	77	± 5		72	± 8	
15	41	25	58	± 6		45	± 5	
	41	25	72	± 7		64	± 4	
	41	25	74	± 7		70	± 8	
20	41	25	87	± 5		85	± 6	
	41	10	80	± 7		59	± 4	
	41	10	97	± 7		75	± 5	
	41	10	92	± 7		92	± 7	
25	41	5	93	± 10		71	± 4	
	41	5	95	± 4		97	± 5	
	42	50	87	± 8		70	± 8	
30	43	50	92	± 7		88	± 4	
	44	50	98	± 4		88	± 5	
	45	50	76	± 7		57	± 3	
35	45	50	68	± 2		66	± 4	
	45	25	93	± 4		87	± 5	
	45	25	83	± 10		78	± 12	
	46	50	79	± 4		77	± 5	
40	47	50	99	± 14		76	± 8	
	48	50	70	± 3		65	± 3	
	48	25	87	± 4		81	± 5	
45	49	50	83	± 5		77	± 7	
	50	50	75	± 5		69	± 5	
	51	50	89	± 7		85	± 8	

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Table 1 (cont'd)

	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level		After 4 hrs.
			After 2 hrs.		
10	52	50	73 ± 3		61 ± 4
	53	100	83 ± 9		80 ± 14
15	53	50	73 ± 4		55 ± 5
	54	50	76 ± 7		74 ± 6
20	55	50	81 ± 3		75 ± 3
	56	50	78 ± 4		72 ± 3
25	56	25	81 ± 8		75 ± 3
	56	10	94 ± 4		97 ± 4
30	57	50	63 ± 6		58 ± 7
	57	50	69 ± 5		63 ± 7
35	57	25	67 ± 7		66 ± 7
	57	25	79 ± 10		70 ± 4
40	57	10	95 ± 3		87 ± 6
	57	5	82 ± 6		68 ± 5
45	58	50	67 ± 2		75 ± 5
	59	50	62 ± 5		59 ± 9
50	60	50	85 ± 4		78 ± 3
	60	50	102 ± 6		81 ± 5
55	60	25	87 ± 7		89 ± 6
	61	50	76 ± 5		61 ± 5
55	61	50	98 ± 8		79 ± 4

The hypoglycemic activity of the compounds of the present invention was confirmed in a second *in vivo* test system; namely, the normal fed rat system. The procedure used in this test system is described below.

Male Sprague Dawley rats (Charles River Laboratories) weighing 175-200 g were used in this test system.

- 45 Test formulations were prepared by suspending the test compound in 5% acacia (concentration of the drug was adjusted such that 0.25 ml/100 g body weight administered orally gave the desired dose on a body weight basis). The desired dose level of each test formulation was administered to four rats by oral gavage at the beginning of the experiment. Blood glucose levels were determined immediately before the first dose and at 3 and 5 hours thereafter by an enzymatic procedure employing glucose oxidase and peroxidase coupled with a chromogenic oxygen acceptor. A mean was taken of the 4 values obtained before the first dose and at the 3 and 5 hour intervals. The 3 and 5 hour mean values, calculated as a percentage of the first dose mean value, are reported in Table 2, below. In Table 2, Column 1 provides the example number of the test compound, Column 2 provides the dose level of compound tested, and Columns 3 and 4 provide a measurement of the test animal's blood glucose level 3 and 5 hours after test compound administration, respectively, as a percentage of the test animal's pre-administration blood glucose level.

TABLE 2

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HYPOLYCEMIC ACTIVITY OF TEST COMPOUNDS IN
NORMAL FED RATS

	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial <u>Blood Glucose Level</u>	
			After 3 hrs.	After 5 hrs.
10	15	167	84	87
	16	200	92	79
	17	200	78	68
	22	200	84	68
15	24	200	100	100
	25	200	100	100
	26	200	100	100
	31	200	95	92
20	32	200	100	96
	38	200	90	74
	41	160	76	67
	45	167	61	63
25	47	200	82	73
	48	167	87	81
	49	200	100	98
	56	150	79	65
30	57	200	84	73
	58	200	100	100
	61	200	89	82
	62	200	78	53
35	63	200	69	52
	64	200	91	89
	65	200	100	91

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Table 2 (cont'd)

	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
			After 3 hrs.	After 5 hrs.
10	66	200	100	86
	67	200	92	88
	68	200	88	89
	69	200	93	88

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The hypoglycemic activity of the compounds of the present invention was confirmed in yet a third *in vivo* test system; namely, the obese diabetic Zucker rat (Zucker Diabetic Fatty Rat) test system. The rats used in this test system were 6 to 8 months old, weighed between 550 to 625 grams and had a pre-drug blood glucose level between 250 to 350 mg/dl. The procedure used in this test system is the same as that described for the normal fed rat test system, above. The results of such tests are set forth in Table 3, below. The format of Table 3 is the same as that used in Table 2.

TABLE 3

HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS IN OBESE DIABETIC ZUCKER RATS				
	Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
			After 3 hrs.	After 5 hrs.
30	22	50	53	56
	45	167	30	20
	47	167	74	66
	56	50	79	66

Finally, the long-term hypoglycemic activity of the compounds of the present invention was tested in yet another *in vivo* test system. This long-term test system entailed incorporating test compound into the test animal's diet at various concentrations (control animal's diet contained no test compound). Such diet was then fed to the test or control animals for either 14 or 21 days. Each test or control animal was then bled from the tail (200-400 μ l sample of blood) at 0 (before diet started), 7, 14 and, if appropriate, 21 and 28 days after diet administration was started. Plasma samples were then obtained from each blood sample collected and the glucose concentration of such plasma samples was determined enzymatically.

The results of the long-term hypoglycemic test system described above are set forth in Table 4, below. In Table 4, Column 1 describes the type of rodent used in the test system, Column 2 provides the example number of the test compound or indicates that the numbers reported are for a control animal, Column 3 provides the concentration, in percent, of test compound in the test or control animal's diet. Columns 4-8 provide the plasma glucose concentration at days 0, 7, 14 and, if appropriate, 21 and 28, respectively, for the animals tested. Glucose lowering was not associated with depressed diet consumption.

TABLE 4

LONG-TERM HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS

Type of Rodent*	Example No. of Compd. Tested	Concentration of Test Compd. in Diet (%)	0	7	14	21	28
ZDF	45	0.1	388	140	155	--	--
ZDF	control	--	416	364	445	--	--
ZDF	45	0.1	464	215	238	285	--
ZDF	45	0.025	467	451	452	517	--
ZDF	control	--	478	499	571	565	--
ZDF	45	0.1	357	171	166	--	--
ZDF	64	0.1	339	187	182	--	--
ZDF	control	--	343	423	454	--	--
ZDF	45	0.1	309	137	142	--	--
ZDF	71	0.1	311	237	232	--	--
ZDF	70	0.1	300	190	195	--	--
ZDF	control	--	317	286	255	--	--
Male AVY/a (Harlan)	45	0.1	438	338	315	287	295
Male AVY/a (Harlan)	38	0.1	340	351	328	303	331
Male AVY/a (Harlan)	control	--	429	414	410	390	359

* ZDF = 8 week old male Zucker Diabetic Fatty rat; AVY/a = viable yellow mouse

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The present invention also provides a method for treating Alzheimer's disease in mammals comprising ad-

ministering a therapeutically effective amount of a compound of formula Ia. The term "therapeutically effective amount", as defined for this method, means the amount of compound necessary to reduce, eliminate or prevent the physiological effects or causes of Alzheimer's disease following administration, preferably to a human suffering from or susceptible to Alzheimer's disease.

5 Alzheimer's disease is a degenerative disorder of the human brain. Clinically, it appears as a progressive dementia. Its histopathology is characterized by degeneration of neurons, gliosis, and the abnormal deposition of proteins in the brain. Proteinaceous deposits (called "amyloid") appear as neurofibrillary tangles, amyloid plaque cores, and amyloid of the congophilic angiopathy. [For reviews, see, Alzheimer's Disease, (B. Reisberg, ed., The Free Press 1983).]

10 While there is no general agreement as to the chemical nature of neurofibrillary tangles, the major constituent of both the amyloid plaque cores and the amyloid of the congophilic angiopathy has been shown to be a 4500 Dalton protein originally termed β -protein or amyloid A4. Throughout this document this protein is referred to as β -amyloid peptide or protein.

15 β -amyloid peptide is proteolytically derived from a transmembrane protein, the amyloid precursor protein (APP). Different splice forms of the amyloid precursor protein are encoded by a widely expressed gene. see, e.g., K. Beyreuther and B. Müller-Hill, Annual Reviews in Biochemistry, 58:287-307 (1989). β -amyloid peptide consists, in its longest forms, of 42 or 43 amino acid residues. J. Kang, et al., Nature (London), 325:733-736 (1987). These peptides, however, vary as to their amino-termini. C. Hilbich, et al., Journal of Molecular Biology, 218:149-163 (1991).

20 Because senile plaques are invariably surrounded by dystrophic neurites, it was proposed early that β -amyloid peptide is involved in the loss of neuronal cells that occurs in Alzheimer's disease. B. Yankner and co-workers were the first to demonstrate that synthetic β -amyloid peptide could be neurotoxic *in vitro* and *in vivo*. B. A. Yankner, et al., Science, 245:417 (1989); see also, N. W. Kowall, et al., Proceedings of the National Academy of Sciences, U.S.A., 88:7247 (1991). Other research groups, however, were unable to consistently demonstrate direct toxicity with β -amyloid peptide. see, e.g., Neurobiology of Aging, 13:535 (K. Kosik and P. Coleman, eds. 1992). Even groups receiving β -amyloid peptide from a common source demonstrate conflicting results. D. Price, et al., Neurobiology of Aging, 13:623-625 (1991) (and the references cited therein).

25 As mentioned *supra*, cells have alternative mechanisms for processing APP which can result in the formation of the β -amyloid protein and subsequently, the senile plaques. It is likely that this alternative processing route occurs in the lysosomes. It has been found that compounds that inhibit lysosomal enzymes inhibit the fragment formation. see, e.g., Science, 155:689 (1992).

30 A lysosome is a membranous reservoir of hydrolytic enzymes responsible for the intracellular digestion of macromolecules. Lysosomes are known to contain approximately forty hydrolytic enzymes, including proteases, nucleases, glycosidases, lipases, phospholipases, phosphatases and sulfatases. These enzymes are all acid hydrolases which are optimally active at about pH 5. Therefore, it is necessary to determine which enzyme or enzymes are responsible for this alternative processing of the APP and the consequent formation of the β -amyloid protein.

35 Abnormally high concentrations of the proteases cathepsins D and B have been observed in the brains of patients with early-onset Alzheimer's disease. Yu Nakamura, et al., Neuroscience Letters, 130, 195-198 (1991). Furthermore, elevated activity for cathepsin D has been observed in the brains of Alzheimer's patients. M. Takeda, et al., Neurochemistry Research, (abstract), 11:117 (1986). Cathepsin D is a lysosomal endopeptidase that is present in all mammalian cells. see, e.g., "Proteinases in Mammalian Cells and Tissues," ed. (A. J. Barret, ed. 1977) pp. 209-248. It is the only aspartyl protease that is known to be a lysosomal enzyme.

40 The cathepsins are a family of hydrolase enzymes that are usually located in the lysosomes. These enzymes are endopeptidases with an acidic optimum pH. Cathepsin A is a serine carboxypeptidase, cathepsin C [EC 3.4.14.1] is a dipeptidyl peptidase, cathepsin D [EC 3.4.23.5] is an aspartyl protease, and cathepsin B₂ [EC 3.4.16.1] is a serine carboxypeptidase. Cathepsin B [EC 3.4.22.1] (also known as cathepsin B₁) and cathepsin L [EC 3.4.22.15] are thiol proteases having activity within the lysosomes.

45 It has been found that inhibition of cathepsin D using an aspartyl protease inhibitor reduces the formation of β -amyloid protein and the resultant senile plaque. As such, compounds which inhibit cathepsins (and, in particular, cathepsin D) or reduce the formation of β -amyloid protein would be expected to be useful in treating Alzheimer's disease. Such activities were demonstrated in the following test systems.

CATHEPSIN D PERCENT INHIBITION ACTIVITY

50 A fluorometric assay was adapted from the method disclosed by Murakami et al., Anal. Biochem. 110:232-239 (1981) for measuring renin activity. Human liver cathepsin D (Athens Research and Technology, Athens, GA) was diluted in assay buffer, 200mM NaOAc, pH 4.5, 150mM NaCl to 500 ng/mL and then 100 μ L of this

cathepsin D solution was added to each well of a 96 well plate with the exception of control wells which received just 100 µL of assay buffer. Compound stocks were prepared by dissolving a sufficient quantity of the particular compound to be tested in DMSO such that a 10 µg/ml concentration of test compound in DMSO was obtained and then 5 µL of the compound stock was added to each of the wells prepared above. Blank and enzyme control wells each received 5 µL of the DMSO vehicle.

Following a ten minute incubation at 25°C to allow enzyme/compound interaction, 5 µL of a 500µM solution of a derivative of a known porcine renin tetradecapeptide fluorometric substrate (Bachem Biosciences, Inc. 1993 Catalog ID No. I-1340; Bachem Biosciences, Philadelphia, PA) in DMSO was added per well to initiate the reaction. After incubation at 37°C for 30 minutes, cathepsin D activity was terminated by the addition of 100 µL per well of 400 mU/mL microsomal leucine aminopeptidase (EC 3.4.11.2, Sigma, St. Louis, MO) in 1M Tris-HCl, pH 8.0.

The plates were then analyzed in a fluorometer (CytoFluor 2350, Millipore, Bedford, MA) with an excitation wavelength of 360nm and an emission wavelength of 460nm, in order to check for background fluorescence due to test compounds. Following a two hour incubation at 37°C, to allow the aminopeptidase to release the fluorophore, 7-amido-4-methylcoumarin (AMC) from the products of cathepsin D cleavage, the plates were again analyzed in the fluorometer. In order to check for potential false positives, i.e., inhibitors of microsomal leucine aminopeptidase, residual aminopeptidase activity was monitored directly in each well by the addition of 20 µL/well of 2.5mM Leu-pNA (Bachem Biosciences, Philadelphia, PA) in 10% DMSO. Aminopeptidase activity was measured as an increase in the absorbance of 405nm in a UV_{max} microplate reader (Molecular Devices, Menlo Park, CA).

Cathepsin D activity was linear under these conditions and the results are expressed as a percentage of the controls in Table 5, below. All results presented are the mean and standard deviation of at least four replicate assays.

25

TABLE 5

CATHEPSIN D INHIBITION ACTIVITY		
	Example No.	% Inhibition of Cathepsin D
30	1	36
	4	50
	5	74
35	6	29
	8	64
	18	38
40	42	88
	45	62
	50	40
45	55	90
	75	43
	76	32
50	77	87
	81	21
	82	79
55	82	68
	83	47

CATHEPSIN D INHIBITION IC₅₀ ACTIVITY

The above assay was repeated with the exception that the compound stocks were prepared in various concentrations other than 10 µg/ml so that IC₅₀ values (concentration of test compound at which 50% inhibition of cathepsin D was obtained) for the test compounds could be determined. The results obtained from such assay system are set forth in Table 6 below.

TABLE 6

	Example No.	IC ₅₀ (Mg/Ml)
10	5	2.6
	28	3.1
15	31	1.6
	35	8.9
20	42	1.6
	47	5.2
25	56	>4.15
	68	3.4
30	68	1.4
	69	2.4
35	71	1.2
	71	4.8
40	77	4.5
	78	25.0
45	79	3.7
	80	47.0

β-AMYLOID PROTEIN PRODUCTION INHIBITION

Two cell lines (human kidney cell line 293 and Chinese hamster ovary cell line CHO) were stably transfected with the gene for APP751 containing the double mutation Lys-651-Met-652 to Asn-651-Leu-652 (APP-751 numbering) commonly called the Swedish mutation using the method described in Citron et al., *Nature* 360:672-674 (1992). The transfected cell lines were designated as 293 751 SWE and CHO 751 SWE, and were plated in Corning 96 well plates at 2.5x10⁴ or 1x10⁴ cells per well respectively in Dulbecco's minimal essential media (DMEM) plus 10% fetal bovine serum. Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide (CO₂), the media were removed and replaced with 200 µL per well of conditioned media (media containing compound stocks; compound stocks diluted with media such that the concentration of DMSO in the media/compound stock solution did not exceed 0.5%) for a two hour pretreatment period during which the cells were incubated as described above. These compound stocks were prepared by dissolving a sufficient quantity of the particular compound to be tested in DMSO such that a 10 µg/ml concentration was obtained. After this pretreatment period, the conditioned media was removed and replaced with fresh conditioned media and the cells were incubated for an additional two hours.

After treatment, plates were centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100 µL of conditioned media were transferred into an ELISA plate precoated with antibody 266 [Seubert et al., *Nature*, 359:325-327 (1992)] and stored at 4°C overnight prior to the completion of the ELISA assay the next day.

Cytotoxic effects of the compounds were measured by a modification of the method of Hansen et al., *J. Immun. Meth.* 119:203-210 (1989). To the cells remaining in the tissue culture plate, was added 25 µL of a 3-

(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) stock solution (5 mg/mL) to a final concentration of 1 mg/mL. Cells were incubated at 37°C for one hour, and cellular activity was stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% DMF, pH 4.7). Complete extraction was achieved by overnight shaking at room temperature. The difference in the OD_{562nm} and the OD_{650nm} was measured in a Molecular Devices UV_{max} microplate reader as an indicator of the cellular viability.

The results of the β-amyloid protein ELISA were fit to a standard curve and expressed as ng/mL β-amyloid protein peptide. In order to normalize for cytotoxicity, these β-amyloid protein results were divided by the cytotoxicity results and expressed as a percentage of the results from a drug-free control.

10

TABLE 7

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β-AMYLOID PROTEIN INHIBITION		
Example No.	% Inhibition of β-Amyloid Protein	
15	5	47
	5	58
	31	58
20	42	52
	70	38
	71	65
25	77	25
	81	100

As can be seen from the data in Tables 5, 6 and 7, the compounds of formula Ia can be administered for prophylactic and/or therapeutic treatment of diseases related to the deposition of β-amyloid protein such as Alzheimer's disease, Down's syndrome, and advanced aging of the brain. In therapeutic applications, the compounds are administered to a host already suffering from the disease. The compounds will be administered in an amount sufficient to inhibit further deposition of β-amyloid protein plaque.

For prophylactic applications, the compounds of formula Ia are administered to a host susceptible to Alzheimer's disease or a β-amyloid protein related disease, but not already suffering from such disease. Such hosts may be identified by genetic screening and clinical analysis, as described in the medical literature. see e.g., Goate, *Nature* 349:704-706 (1991). The compounds will be able to inhibit or prevent the formation of the β-amyloid protein plaque at a symptomatically early stage, preferably preventing even the initial stages of the β-amyloid protein disease.

The compounds of the present invention and the compounds utilized in the methods of the present invention are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.5 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 1.0 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician in light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the chosen route of administration. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally, the compounds may also be administered by a variety of other routes such as the transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

While it is possible to administer a compound of the invention, or a compound used in the methods of this invention, directly, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such formulations will contain from about 0.01 percent to about 90 percent of a compound of the invention.

In making the formulations of the present invention, the active ingredient will usually be mixed with at least one carrier, or diluted by at least one carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the formulations can be in the form of tablets, granules, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium) and soft and hard gelatin capsules.

Examples of suitable carriers, diluents and excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, liquid paraffin, calcium silicate, microcrystalline cellulose, polyvinyl pyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, vegetable oils, such as olive oil, injectable organic esters such as ethyl oleate, talc, magnesium stearate, water and mineral oil. The formulations may also include wetting agents, lubricating, emulsifying and suspending agents, preserving agents, sweetening agents, perfuming agents, stabilizing agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well-known in the art.

For oral administration, a compound of this invention, or a compound used in the methods of this invention, ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent or excipient therefor.

In order to more fully illustrate the operation of this invention, the following examples of formulations are provided. The examples are illustrative only and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

20

FORMULATION 1

Hard gelatin capsules suitable for use in treating Alzheimer's disease or reducing glucose concentration are prepared using the following ingredients:

25

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 5	250 mg	55.0
Starch dried	220 mg	43.0
Magnesium stearate	10 mg	2.0
	460 mg	100.0

35

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

FORMULATION 2

Capsules each containing 20 mg of medicament are made as follows:

40

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 1	20 mg	10.0
Starch	89 mg	44.5
Microcrystalline cellulose	89 mg	44.5
Magnesium stearate	2 mg	1.0
	200 mg	100.0

50

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

FORMULATION 3

55

Capsules each containing 100 mg of active ingredient are made as follows:

	Amt. per Capsule	Concentration by Weight (percent)
5	Compound of Example No. 45	100 mg 29.0
	Polyoxyethylenesorbitan monooleate	50 mcg 0.02
	Starch powder	250 mg 71.0
		<u>250.05 mg</u> <u>100.02</u>

10 The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

FORMULATION 4

Tablets each containing 10 mg of active ingredient are made up as follows:

	Amt. per Capsule	Concentration by Weight (percent)
15	Compound of Example No. 71	10 mg 10.0
20	Starch	45 mg 45.0
	Microcrystalline cellulose	35 mg 35.0
25	Polyvinyl pyrrolidone (as 10% solution in water)	4 mg 4.0
	Sodium carboxyethyl starch	4.5 mg 4.5
	Magnesium stearate	0.5 mg 0.5
30	Talc	1 mg 1.0
		<u>100 mg</u> <u>100.0</u>

35 The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°-60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

FORMULATION 5

40 A tablet formula may be prepared using the ingredients below:

	Amt. per Capsule	Concentration by Weight (percent)
45	Compound of Example No. 2	250 mg 38.0
50	Cellulose microcrystalline	400 mg 60.0
	Silicon dioxide fumed	10 mg 1.5
	Stearic acid	5 mg 0.5
		<u>665 mg</u> <u>100.0</u>

55 The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION 6

Suspensions each containing 5 mg of medicament per 40 ml dose are made as follows:

	Per 5 ml of suspension
5	Compound of Example No. 59 5 mg
10	Sodium carboxymethyl cellulose 50 mg
15	Syrup 1.25 ml
	Benzoic acid solution 0.10 ml
	Flavor q.v.
	Color q.v.
	Water q.s. to 5 ml

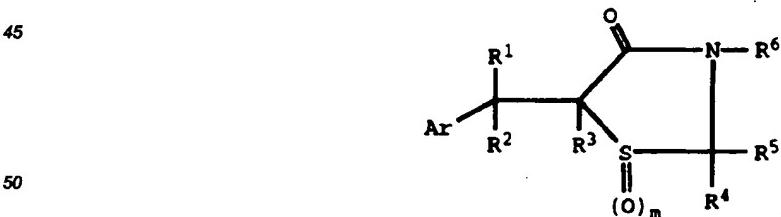
The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl-cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

FORMULATION 7

An aerosol solution is prepared containing the following components:

	Concentration by Weight (%)
25	Compound of Example No. 53 0.25
30	Ethanol 29.75
	Propellant 22 (Chlorodifluoromethane) 70.00
	<hr/> 100.00

35 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

40 Claims**1. The use of a compound of the formula**

wherein:

55 Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkyloxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)₂ or -N(R⁷)SO₂R⁷, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-

benzofuranyl, (v) 2- or 3- benzothiophenyl, (vi) 2- or 3- thiienyl, (vii) 2-, 3- or 4- pyridyl, (viii) 2- or 3- furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3- indolyl or (xiii) N-substituted 2- or 3- indolyl;

5 R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

R² and R³ are each hydrogen or when taken together form a bond;

10 R⁴ and R⁵ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁵ is hydrogen, the other is -SCH₃;

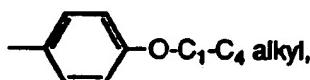
15 R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃, or -(CH₂)_p-Y where P is 0, 1, 2 or 3 and Y is cyano, -OR⁸,



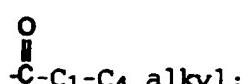
15

tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio, or

20



25



where R⁸ is hydrogen, C₁-C₄ alkyl, or

30

R⁹ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₈ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl), where q is an integer from 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

35 m is 0, 1, or 2;

with the provisos that

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

40

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring; when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R¹ must be hydrogen;

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Ar cannot be phenyl substituted solely with two hydroxy substituents; and when R⁴ and R⁵ are each hydrogen, R⁶ cannot be C₁-C₆ alkyl, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for reducing blood glucose concentrations in mammals.

2.

A use of Claim 1 which employs a compound wherein m is 0; R⁴ and R⁵ taken together are =S; R¹ is hydrogen; R⁶ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl; and Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, trifluoromethyl, C₁-C₄ alkylthiophenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkyloxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 2-, 3- or 4- pyridyl, or (iv) 2- or 3- furanyl.

3.

A use of Claim 2 wherein the compound employed is 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

4.

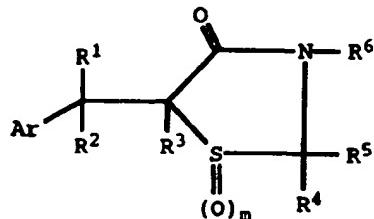
A pharmaceutical formulation adapted for reducing blood glucose concentrations comprising a compound as set forth in any one of Claims 1 through 3, admixed with one or more pharmaceutically acceptable

carriers, diluents or excipients therefor.

5. The use of a compound of the formula

5

10



wherein:

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Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, trifluoromethyl, C₁-C₄ alkylphenyl, phenyl, NO₂, F, Cl, hydroxy, phenoxy, C₁-C₄ alkylthiophenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)₂ or -N(R⁷)SO₂R⁷, where each R⁷ is independently hydrogen or C₁-C₆ alkyl or (iii) 1- or 2-naphthyl;

20

R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

R² and R³ are each hydrogen or when taken together form a bond;

R⁴ and R⁶ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁶ is hydrogen, the other is -SCH₃;

25

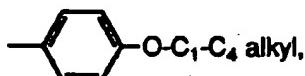
R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃, or (CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR⁸,

30



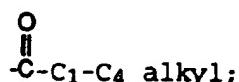
tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio, or

35



where R⁸ is hydrogen, C₁-C₄ alkyl, or

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R⁹ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl), where q is an integer from 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

50

m is 0, 1, or 2;

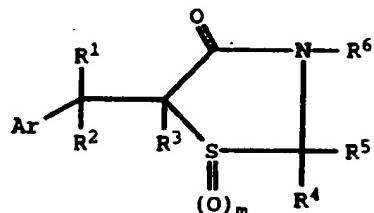
or a pharmaceutically acceptable salt thereof, to prepare a medicament useful in treating Alzheimer's disease.

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6. A use of Claim 5 which employs a compound wherein m is 0; R⁴ and R⁶ taken together are =S; R¹ is hydrogen; R⁶ is hydrogen, C₁-C₆ alkyl, or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, phenyl or C₁-C₄ alkylphenyl; and Ar is phenyl substituted with from one to three substituents independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, F, Cl, hydroxy, phenoxy, C₁-C₄ alkylthiophenyl, -N(R⁷)SO₂R⁷ or -N(R⁷)₂, where each R⁷ is independently

hydrogen or C₁-C₆ alkyl.

7. A use of Claim 6 wherein the compound employed is selected from 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-hexoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[[3-(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[[4-(dimethylamino)phenyl]methylene]-2-thioxo-4-thiazolidinone or pharmaceutically acceptable salts thereof.
8. A pharmaceutical formulation adapted for treatment of Alzheimer's disease comprising a compound as set forth in any of Claims 5 through 7, admixed with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.
9. A compound of the formula



wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, trifluoromethyl, C₂-C₄ alkylphenyl, NO₂, F, Cl, phenoxy, C₁-C₄ alkoxyphenyl, thiophenyl, C₁-C₄ alkylthiophenyl, -COOR⁷, -N(R⁷)₂ or -N(R⁷)SO₂R⁷, where each R⁷ is independently hydrogen or C₁-C₆ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2-, 3- or 4-pyridyl, (viii) 2- or 3-furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3-indolyl or (xiii) N-substituted 2- or 3-indolyl;

R¹ is C₁-C₆ alkyl, C₁-C₄ alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or C₁-C₄ alkylthio;

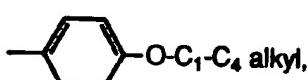
R² and R³ are each hydrogen or when taken together form a bond;

R⁴ and R⁵ are each hydrogen or when taken together are =S, or when one of R⁴ and R⁵ is hydrogen, the other is -SCH₃;

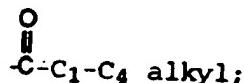
R⁶ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₂-C₆ alkenyl, -SO₂CH₃, or -(CH₂)_p-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR⁸,



tetrazolyl, -NR¹⁰R¹¹, -SH, C₁-C₄ alkylthio, or



where R⁸ is hydrogen, C₁-C₄ alkyl, or



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R⁹ is hydrogen, C₁-C₄ alkyl or NH₂; and R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl, C₁-C₄ alkylphenyl, -(CH₂)_qOH, -(CH₂)_qN(C₁-C₄ alkyl)₂, or -(CH₂)_qS(C₁-C₄ alkyl), where q is an integer from 1 to 6, both inclusive, or R¹⁰ and R¹¹, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

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m is 0, 1, or 2;

with the provisos that

when Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, F, Cl, trifluoromethyl, phenoxy, C₁-C₄ alkyloxyphenyl, C₁-C₈ alkylthio, NO₂, -N(R⁷)₂ or -COOR⁷, where each R⁷ is independently hydrogen or C₁-C₈ alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3- benzofuranyl, (v) 2- or 3- benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2- or 3-indolyl, (viii) 2- or 3-furanyl, (ix) 2-, 3- or 4-pyridyl or (x) quinolinyl; R¹ is hydrogen or C₁-C₆ alkyl; R² and R³ taken together form a bond; m is 0; and R⁴ and R⁵ taken together are =S; R⁶ must be other than hydrogen or C₁-C₆ alkyl;

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when Ar is phenyl; R¹ is hydrogen, methyl or ethyl; R² and R³ taken together form a bond; m is 0; R⁴ and R⁵ taken together are =S; R⁶ must be other than phenyl or C₁-C₄ alkylphenyl;

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R¹ must be hydrogen;

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Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring; and

when R⁴ and R⁵ are each hydrogen, R⁶ cannot be C₁-C₆ alkyl;
and the pharmaceutically acceptable salts thereof.

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10. The compound 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

11. The compound 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

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12. A pharmaceutical formulation comprising a compound of any one of Claims 9 through 11 associated with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

13. A process for preparing a compound as set forth in any of Claims 9-11 which comprises:

(A) reacting a compound of the formula

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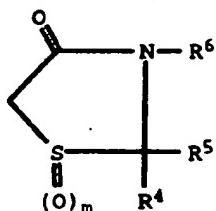
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wherein:

B is O or NH and Ar and R¹ are as defined in any one of Claims 9, 10 or 11, with a compound of the formula

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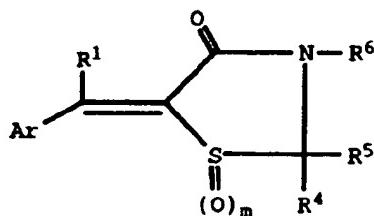
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wherein:

R⁴, R⁵, m and R⁶ are as defined in any one of Claims 9, 10 or 11, so as to provide a compound of the formula

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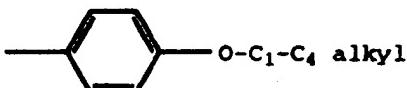
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- (B) reducing a compound of Claim 9 wherein R⁴ and R⁵ taken together are =S so as to prepare a compound of Claim 9 in which R⁴ and R⁵ are hydrogen;
- (C) reducing a compound of Claim 9 in which R² and R³ taken together form a bond so as to prepare a compound of Claim 9 in which R² and R³ are hydrogen;
- (D) reducing a compound of Claim 9 in which R² and R³ taken together form a bond and R⁴ and R⁵ taken together are =S so as to prepare a compound of Claim 9 in which R², R³, R⁴ and R⁵ are all hydrogen;
- (E) alkylating a compound of Claim 9 in which R⁶ is hydrogen so as to prepare a compound of Claim 9 in which R⁶ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl or -(CH₂)_p-Y (where p is an integer from 0 to 3, both inclusive, and Y is cyano, OR⁸, -SH, C₁-C₄ alkylthio, -NR¹⁰R¹¹ or

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where R⁸ is as defined in Claim 9;

- (F) acylating a compound of Claim 9 in which R⁶ is hydrogen so as to prepare a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, where p is an integer from 0 to 3, both inclusive, and Y is

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where R⁹ is as defined in Claim 9;

- (G) oxidizing a compound of Claim 9 wherein m is 0, so as to prepare a compound of Claim 9 wherein m is 1;

(H) oxidizing a compound of Claim 9 wherein m is 0, so as to prepare a compound of Claim 9 wherein m is 2;

(I) oxidizing a compound of Claim 9 wherein m is 1, so as to prepare a compound of Claim 9 wherein m is 2;

(J) reacting a compound of the formula

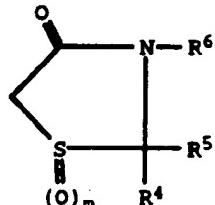


wherein:

B is O or NH and Ar and R¹ are as defined in Claim 9, with a compound of the formula

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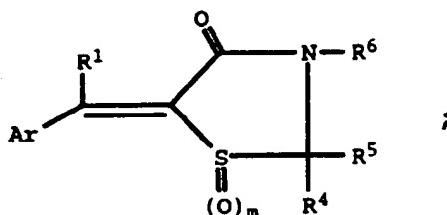


wherein

20 R⁴, R⁵ and m are as defined in Claim 9, and R⁶ is -(CH₂)_p-Y (where p is an integer from 0 to 3, both inclusive, and Y is OR⁸, where R⁸ is hydrogen) so as to provide a compound of the formula

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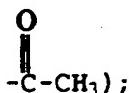
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wherein:

Ar, R¹, R⁴, R⁵ and m are as set forth in Claim 9 and R⁶ is -(CH₂)_p-Y (where p is an integer from 0 to 3, both inclusive, and Y is OR⁸, where R⁸ is

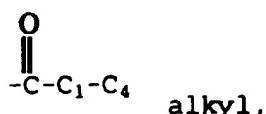
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(K) reducing a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is OR⁸, where R⁸ is

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so as to prepare a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is OR⁸, where R⁸ is hydrogen;

(L) reacting a compound of the formula set forth in Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is OR⁸, where R⁸ is tosyl, with an amine of the formula HNR¹⁰R¹¹ (where R¹⁰ and R¹¹ are as defined in Claim 9) so as to prepare a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is -NR¹⁰R¹¹;

(M) treating a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is cyano with tri-n-butyl tin azide so as to prepare a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y, wherein p is 0 to 3, both inclusive, and Y is tetrazolyl;

(N) reacting a compound of the formula



wherein:

B is O or NH and Ar and R¹ are as defined in Claim 9, with a compound of the formula

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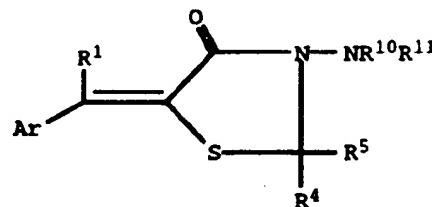
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wherein:

R¹⁰ and R¹¹ are as set forth in Claim 9, so as to provide a compound of the formula

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wherein R⁴ and R⁵ taken together are =S and Ar, R¹, R¹⁰ and R¹¹ are as defined in Claim 9;
 (O) heating a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y wherein p is 0 to 3, both inclusive, and Y is -NR¹⁰R¹¹ (neither of R¹⁰ or R¹¹ being hydrogen) in an ethanol/water mixture in the presence of a catalyst so as to prepare a compound of Claim 9 in which R⁶ is -(CH₂)_p-Y wherein p is 0 to 3, both inclusive, and Y is -NR¹⁰R¹¹ (where one of R¹⁰ and R¹¹ is hydrogen and the other is not hydrogen);
 (P) saponifying a compound of any one of Claims 9 through 11 by reacting the non-salt form of the compound with either a strong acid or a strong base.

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(54) Thiazolidinone derivatives as hypoglycemic agents and for treating Alzheimer's disease.

(57) Provided are methods for treating hyperglycemia and Alzheimer's disease utilizing certain rhodanine derivatives. Certain of the rhodanine derivatives utilized in the instant methods are novel and, accordingly, such compounds, process for preparing same and pharmaceutical formulations thereof, are also provided.

EP 0 587 377 A3



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EUROPEAN SEARCH REPORT

Application Number

EP 93 30 6959 3

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.CLS)						
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim							
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X	EP-A-0 398 179 (NNISSHIN FLOUR MILLING CO LTD) * claims * ---	1-4,9-13							
X	EP-A-0 047 109 (ONO PHARMACEUTICAL) * claims 1,4,5,54-119 * ---	1-4,9-13							
X	EP-A-0 045 165 (ONO PHARMACEUTICAL CO LTD) * claims 1,21-25 * ---	1-4,9-13							
X	CHEMICAL ABSTRACTS, vol. 116, no. 3, 20 January 1992, Columbus, Ohio, US; abstract no. 20983q, LI DUXIN ET AL. 'Synthesis of 5-benzylidene-3-carboxymethyl rhodanine' page 572 ; * abstract * & SHANXI DAXUE XUEBAO ZIRAN KEXUEBAN, vol.13, no.1 pages 51 - 55 ---	1-4							
D,X	EP-A-0 391 644 (ELI LILLY AND COMPANY) * claims * ---	9-13							
D,X	EP-A-0 343 643 (WARNER-LAMBERT COMPANY) * claims * ---	9-13							
X	DE-A-40 27 038 (WELLA AG) 5 March 1992 * claims 6-10 * ---	9-13							
X	EP-A-0 449 216 (WARNER-LAMBERT COMPANY) * claims 1-7 * ---	9-13							
		-/-							
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>25 July 1994</td> <td>Theuns, H</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	25 July 1994	Theuns, H
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THE HAGUE	25 July 1994	Theuns, H							
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document							



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Application Number
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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	EP-A-0 211 670 (ELI LILLY AND COMPANY) * the whole document * ---	5-8	
X	CHEMICAL ABSTRACTS, vol. 69, 1968, Columbus, Ohio, US; abstract no. 42531d, * abstract * & KHIM.-PHARM. ZH., vol.2, no.5, 1968 pages 24 - 28 L. YA-LADNAYA ET AL. 'Synthesis and study of rhodamines with potential psychostimulating effect' ---	5-8	
X	EP-A-0 304 493 (KANEKA FUCHI KAGAKU KOGYO KK.) * page 33, line 35 - page 34, line 17 * ---	5-8	
X	CURR. SCI., vol.49, no.12, 20 June 1980 pages 455 - 456 R. AGARWAL ET AL. 'Synthesis and CNS activity of 5-arylidene-3-arylaminoethyl- 4-thiazolidinon-2-thiones' * the whole document * ---	5-8	TECHNICAL FIELDS SEARCHED (Int.CLS)
X	ACTA PHARM. JUGOSLAV., vol.36, no.3, 1986 pages 311 - 317 M.I. HUSAIN ET AL. 'Synthesis and pharmacological studies of some 3-(N,N-disubstituted aminomethyl(-5-(fluor obenzylidene)-4-oxo-thiazolidin-2-thiones' * the whole document * ---	5-8 -/--	
The present search report has been drawn up for all claims			
Place of search	Date of compilation of the search	Examiner	
THE HAGUE	25 July 1994	Theuns, H	
CATEGORY OF CITED DOCUMENTS		I : theory or principle underlying the invention E : earlier patent document, not published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	
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Application Number
EP 93 30 6959

DOCUMENTS CONSIDERED TO BE RELEVANT			
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X	<p>DATABASE WPI Derwent Publications Ltd., London, GB; AN 91-031957 & JP-A-2 300 119 (KANEKA FUCHI CHEM KK.) * abstract *</p> <p>---</p>	5-8	
A	<p>INDIAN DRUGS, vol.21, no.3, 1983 pages 90 - 95 R.R. MOHAN ET AL. 'Synthesis & pharmacological screenings of 2-thio-3-aryl aminomethyl-4-oxo-5-(3,4-disubstituted benzylidene) thiazolidines' * abstract *</p> <p>-----</p>	5-8	
TECHNICAL FIELDS SEARCHED (Int.Cl.)			
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	25 July 1994	Theuns, H	
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